37 CFR 1.135. The fee under 37 CFR 1.17 should be charged to our Deposit Account No. 50-2215.

REMARKS

All pending claims have been rejected under 35 U.S.C. 103 over Hedner in view of LaRoche. This rejection is respectfully traversed.

Hedner relates to treating sleep disordered breathing, including sleep apnoea, with topiramate. LaRoche is a review of antiepileptic drugs and includes disclosure relating to mechanisms of action with respect to epileptic effect . The Office Action explains that the rationale of the rejection is that topiramate and zonisamide are both antiepileptic agents having a common mechanism of action and therefore a skilled person would be motivated to substitute one for the other when treating sleep apnoea with a reasonable expectation of success. It is respectfully submitted that this rationale is not valid for reasons which will now be discussed.

First, zonisamide, topiramate, and other antiepileptic drugs lack a common structural element, as illustrated in the previously submitted Formula Sheet. That means their pharmaceutical effect, antiepileptic or otherwise, cannot be predicted with a reasonable expectation of success from their structure.

Second, if two agents has identical mechanisms of action, a skilled person may have a reasonable expectation of success for predicting a substitution of one for the other would be effective, absent other factors. However, that is not the present situation here since LaRoche teaches that zonisamide and topiramate do not have identical mechanisms of action.

Third, stating that the two drugs have "a common mechanism of action" is an overstatement because it focuses only on similarities and ignores both the differences and the question of whether those similarities are relevant to the issue being considered.

Fourth, if the relevant mechanism of action of two agents were the same, a skilled person would have a reasonable expectation of success for substituting one for the other. That, of necessity, requires that the skilled person knows what is the relevant mechanism of action constitutes. If relevant mechanism of action is not known, there can be no reasonable expectation of success. The record about what is known here is limited to the Hedner reference, and a Declaration by Hedner and two other inventors, and does not establish any particular mechanism is relevant.

The Hedner reference states at page 2, line 14 that the "patophysiology of OSA is virtually unknown." In a paragraph beginning at page 4, line 28, which clearly indicates that the discussion is only speculation by stating at the top of page 5 that "it must be emphasized that ["scientifically attractive explanations for the observed effect of topiramate" in treating OSA] must not be considered binding in any way on the concept or the working of the present invention", it is said that the effect of topiramate "may be due to one or more" of its pharmacological actions, or that "a single action or several of these actions in concert may" increase respiratory neurones drive or their firing. The fact that this is speculation is also indicated by the use of the word "may" rather than "is." The paragraph continues by noting that studies which were not direct to OSA indicated that topiramate's action in the body included (1) modulation of sodium channel conductance, (2) modulation of sodium calcium channel conductance, (3) GABA potentiation, (4) glutamate antagonism, and (5) enzyme (carbonic anhydrase) inhibition.

Even if it were assumed that the relevant mechanism of action was found within this paragraph of the reference, and the Hedner reference explicitly warns against making

that assumption, that would mean there were many possibilities for the relevant mechanism of action, but which was correct was unknown. Looking only at the Hedner reference, there is an insufficient basis for concluding that a skilled person would have a reasonable expectation of identifying the relevant mechanism of action.

Even as to epilepsy where both compounds are known to be active, it is not known whether they are active because of a same mechanism of action. LaRoche teaches the known active agents have a highly variable and different mechanism of action. Those include sodium channel blockade, calcium channel blockade, potentiation of GABA activity and antagonism of glutamate. The figure on page 607 of LaRoche shows that topiramate exhibits all four of these, namely, effecting sodium channels, calcium channels, GABA potentiation and glutamate antagonism. Zonisamide, on the other hand, exhibited effects on sodium and calcium channels only. If LaRoche is being taken to suggest a disclosure of the mechanism each disclosed compound uses to treat epilepsy, it means topiramate and zonisamide have a different mechanisms of action even in treating epilepsy. But that approach is flawed because LaRoche shows that looking at mechanism of action is not valuable for predicting activity since it discloses that tigabine's mechanism of action is GABA activity, and not sodium and/or calcium activity, yet this compound is an effective anticonvulsant. These facts detract from, if not destroy, the possibility that a reasonable expectation of success could exist when treating a different malady.

The rejection ignores these considerations by noting that both topiramate and zonisamide act as anti-convulsants by way of blocking sodium as well as T-type calcium channels. Jan Hedner and his co-inventors have filed a Declaration stating that they were not aware of any knowledge in the art which even suggested that blocking sodium and T-type calcium channels was useful in the treatment of OSA. Coupled with the clear speculation in Hedner's article, it is clear any comments about possible mechanisms

cannot serve to identify the relevant mechanism of action. Neither the references themselves nor any of the Office Action in this case indicate that a person skilled in this art either knew or believed such blocking was the relevant mechanism of action. It is respectfully submitted that this is a critical deficiency, and one which the current Office makes no attempt to remedy. The hypothesized reasonable expectation of success is based only on silence, and that is not permissible. *In re Newell*, 13 USPQ2d 1248, 1250 (Fed. Cir. 1989)("Obviousness cannot be predicted on what is unknown."); *In re Burt*, 148 IUSPQ 548, 553 (CCPA 1966). Topiramate may useful to treat OSA but there is nothing which indicates to a person skilled in the art, how or why that result is achieved. Coupled with the fact that zonisamide does not have the identical mechanism of action as topiramate, there is nothing which allows the skilled person to be motivated to make a substitution or to have a reasonably expectation of success, much less both.

Even if the mechanism assertion in the Office Action was not speculation had some basis, and it does not, the record here establishes that the assertion is wrong. The theory of the rejection is that because both drugs are effective for one type of activity (anti-convulsants) and act by way of blocking sodium as well as T-type calcium channels means a person needing a different type of activity will react in the same way to both drugs . However, the test results discussed in the last response show the theory is wrong. Three of the 4 patients responded to one drug but not the other. Two patients responded to zonisamide but not to topiramate while the opposite was found in one patient. The fourth patient responded to both therapies.

Patient number	1	2	3	4
Zonisamide	+	+	+	-
Topiramate	-	-	+	+

The point of submitting this data was that it clearly shows that effects of these two compounds are unique and that an effect with one of the compounds does not imply or suggest that the other agent is effective. It also shows that antiepileptic activity commonality does not reasonably permit a prediction with a reasonable expectation of success that zonisamide will be active because topiramate is active. The Office Action notes the difference in dosages but even taking that difference into account, the results still establish that the assumption is wrong. Since the dose of zonisamide was double that of topiramate, then there should always be a response to zonisamide when there was a response to the lesser amount of topiramate if, as is being assumed, both are acting by the same mechanism. The test results show that the same response did not always occur.

All of the foregoing considerations establish that zonisamide represents a novel, unpredictable, unobvious and unique therapeutic modality in sleep apnea. In view thereof, applicant believes the pending application is in condition for allowance.

Dated: May 18, 2009

Respectfully submitted,

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